REMARKS

New claim 12 has been added to the specification. Support for claim 12 may be found in the Examples of the specification, in particular with the sequences designated as D4 and D5. The sequences D4 and D5 further support the amendments to the claims and page 8, final 7 lines of the specification. No new matter has been added with these amendments or new claim 12. As such, entry thereof is respectfully requested.

Rejections under 35 U.S.C. §112, first paragraph

The Examiner rejects claims 2-6 and 8-11 under 35 U.S.C. §112, first paragraph for lack of written description. The Examiner states,

> Applicants claim a soluble Fas ligand, which inhibits Fas-mediated apoptosis. This broad claim reads on all possible Fas ligands that are capable of being a pro-apoptotic agent.

Applicants traverse this rejection and withdrawal thereof is respectfully requested.

The present invention, as encompassed by claim 2 is drawn to an isolated polypeptide

1) having an amino acid sequence of natural human Fas ligand

2) wherein the 129th amino acid and 130th amino acid residues as measured from N terminal end are both deleted,

3) and at least one amino acid residue from 111th amino acid to 128th amino acid residues or at least one amino acid residue from 131st amino acid to 133rd amino acid residues as measured from N terminal end is deleted.

Independent claims 3, 10 and 11 also recite various features defining the derivative of human Fas ligand polypeptide of the invention. The full Fas ligand sequence was known prior to the present invention as evidenced by the attached excerpt from the NCBI web site, which lists the full Fas ligand sequence as of April 14, 1995. Thus, by recitation of "natural human Fas ligand" one skilled in the art would have been well aware of the sequence being recited.

The Examiner bases the rejection on the statement that "Applicants claim a soluble Fas ligand, which inhibits Fas-mediated apoptosis." However, the Examiner has ignored the numerous other features recited in the claims and apparently misunderstands the nature of the invention. Reconsideration of the claims and withdrawal of the rejection are respectfully requested.

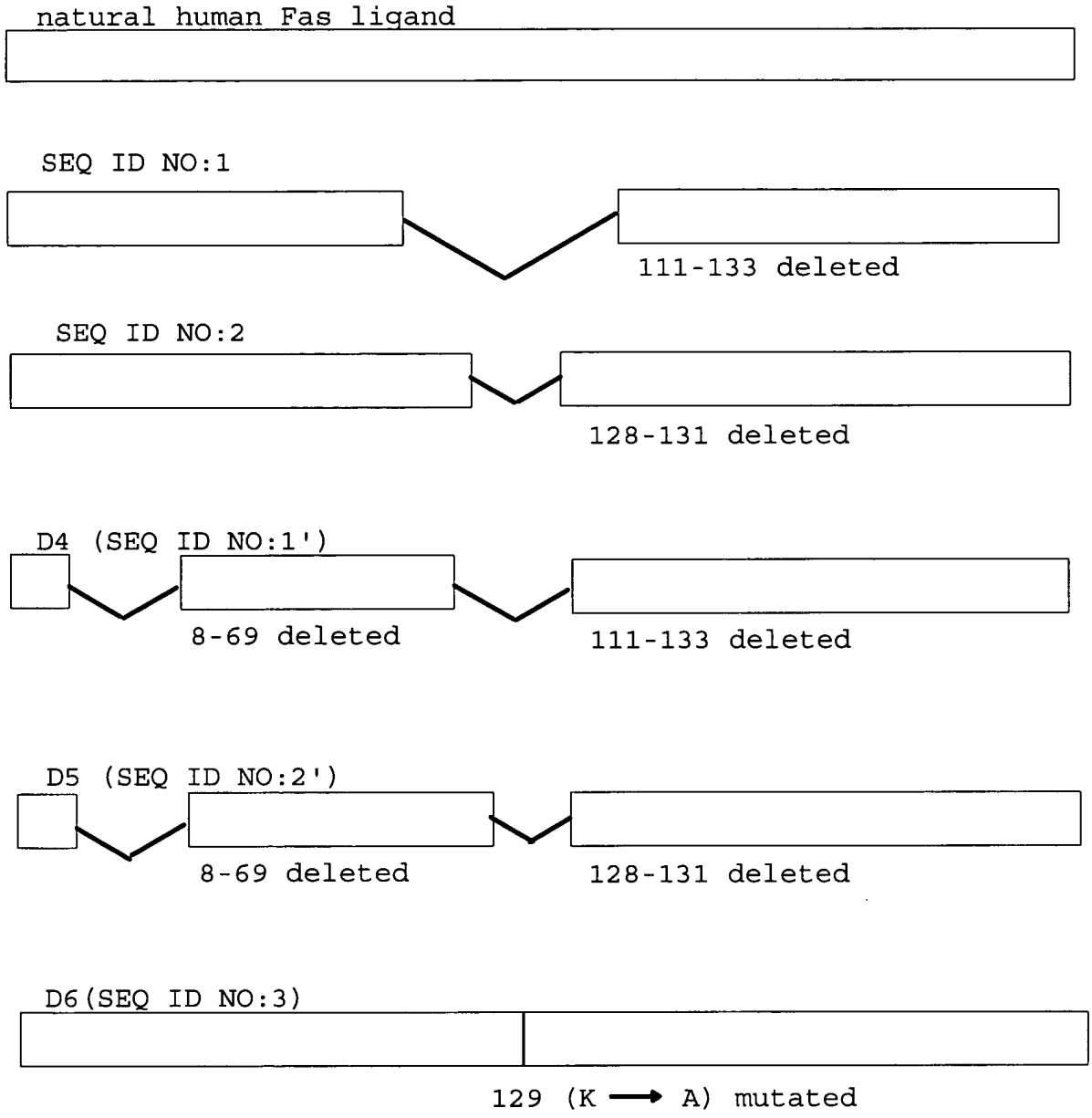
As indicated above, the Examiner states, in part, "Applicants claim a soluble Fas ligand...." This statement indicates a misunderstanding of the invention. The present claims encompass two embodiments of the invention: a first embodiment of a human Fas ligand derivative (claims 2-5 and 8-11) and a second embodiment of a soluble Fas ligand (claim 6 only).

Thus, the Examiner's rejection is at best only applicable to claim 6. Claim 6 has been further amended to define the soluble Fas ligand as comprising the amino acid sequence represented from Gln of the 130th amino acid to the C terminal amino acid residue as measured from the N-terminal end of natural human Fas ligand. The invention of claim 6 has thus been defined as being a

specific portion of the natural human Fas ligand. As such, claim 6 is very narrowly drawn to a soluble polypeptide comprising a specific sequence, which is fully described in the specification. Withdrawal of the rejection regarding claim 6 is therefore also requested.

The Examiner further states in the rejection that Applicants are only in possession of the Fas ligand derivatives of SEQ ID NO:1 and SEQ ID NO:2. This statement represents a further misunderstanding of the invention. The working Examples of the specification describe the Fas ligand derivative D4 (SEQ ID NO:1', wherein the 8^{th} through 69^{th} amino acid residues as measured from the N-terminal end have been deleted from SEQ ID NO:1) and the Fas ligand derivative D5 (SEQ ID NO:2', wherein the 8^{th} through 69^{th} amino acid residues have been deleted from SEQ ID NO:2).

The six Fas ligand sequences discussed in the specification are as follows:



The present inventors have found that at least the deletion or substitution of the amino acid residues between Lys 129 and Gln 130 in the amino acid sequence of natural Fas ligand is necessary to create protease resistant Fas ligand derivatives. The present inventors have also determined that at least one amino acid deletion or substitution from the 111^{th} to 133^{rd} amino

acid residues in the natural Fas ligand results in the same protease resistant Fas ligand derivatives. These findings are supported in the working examples of the specification. Namely, the following three different types of mutants were studied for resistivity to protease cleavage. With the following three mutants, the protease cleavage site of Fas ligand was thoroughly studied.

D4(SEQ ID NO:1') - amino acids 8-69 and 111-133 deleted

D5(SEQ ID NO:2') - amino acids 8-69 and 128-131 deleted

D6(SEQ ID NO:3) - amino acid 129 (K $\rightarrow$ A) mutated

As noted by the Examiner, applicants are not required to disclose every species encompassed by a genus, but only so much as is required to support the described invention. The above-described mutants fully support the described invention. As such, the Examiner is requested to consider all of the recited features of the invention and withdraw the rejection.

Rejections under 35 U.S.C. 112, second paragraph

The claims have been rejected under 35 U.S.C.§112, second paragraph with the indication that the term "novel" must be deleted from the claims and replaced with "isolated" or "purified." The claims have been amended as requested by the Examiner to recite "An isolated polypeptide...." As such, withdrawal of the rejection is respectfully requested.

As the above-indicated amendments and remarks address and overcome the objections and rejections of the specification and

claims, withdrawal of the objections and rejections and allowance of the claims are respectfully requested.

Should the Examiner have any questions regarding the above-indicated application she is requested to please contact MaryAnne Armstrong, PhD (Reg. No. 40,069) in the Washington DC area at (703) 205-8000.

A marked-up version of the amended claims showing all changes is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____

Gerald M. Murphy, Jr., #28,977

MaryAnne Armstrong, PhD, #40,069

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

GMM/MAA
1110-266P

Attachment: Version with Markings to Show Changes Made
Print out from NCBI database, showing Fas ligand sequence

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Claims 2, 3, 6, and 10-12 have been amended as follows.

2. (Thrice amended) ~~A novel~~ **An isolated** polypeptide having an amino acid sequence of natural human Fas ligand wherein the 129th amino acid and 130th amino acid residues as measured from N terminal end are both deleted ~~or substituted~~, and at least one amino acid residue from 111th amino acid to 128th amino acid residues or at least one amino acid residue from 131st amino acid to 133rd amino acid residues as measured from N terminal end is deleted ~~or substituted~~.

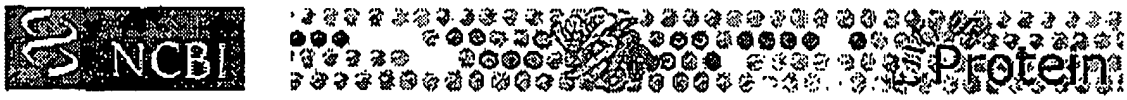
3. (Thrice Amended) ~~A novel~~ **An isolated** polypeptide having an amino acid sequence of natural human Fas ligand wherein all of the 8th amino acid to 69th amino acid residues as measured from N terminal end are deleted, 129th amino acid and 130th amino acid residues as measured from N terminal end are both deleted ~~or substituted~~, and at least one amino acid residue from 111th amino acid to 128th amino acid residues or at least one amino acid residues from 131st amino acid to 133rd amino acid residues as measured from N terminal end is deleted ~~or substituted~~.

6. (Twice Amended) A soluble Fas ligand which inhibits Fas-mediated apoptosis **and which comprises the amino acid sequence represented from Gln of the 130th amino acid to C terminal amino acid residue as measured from N-terminal end of natural human Fas ligand**.

10. (Thrice amended) ~~A novel~~ **An isolated** polypeptide having an amino acid sequence of natural human Fas ligand wherein the 129th amino acid and 130th amino acid residues as measured from N terminal end are both deleted ~~or substituted~~, and at least one amino acid residue from 111th amino acid to 128th amino acid residues or at least one amino acid residue from 131st amino acid to 133rd amino acid residues as measured from N terminal end is deleted ~~or substituted~~, wherein said ~~novel~~ polypeptide has membrane binding activity and induces Fas-mediated apoptotic activity.

11. (Thrice amended) ~~A novel~~ **An isolated** polypeptide having an amino acid sequence of natural human Fas ligand wherein all of the 8th amino acid to 69th amino acid residues as measured from N terminal end are deleted, 129th amino acid and 130th amino acid residues as measured from N terminal end are both deleted ~~or substituted~~, and at least one amino acid residue from 111th amino acid to 128th amino acid residues or at least one amino acid residues from 131st amino acid to 133rd amino acid residues as measured from N terminal end is deleted ~~or substituted~~, wherein said ~~novel~~ polypeptide has membrane
binding activity and induces Fas-mediated apoptotic activity.

New claim 12 has been added.



1: AAC50124. Fas ligand...[gi:595431]

LOCUS AAC50124 281 aa linear PRI 14-APR-1995
DEFINITION Fas ligand.
ACCESSION AAC50124
VERSION AAC50124.1 GI:595431
DBSOURCE locus HSU11821 accession U11821.1
KEYWORDS .
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (residues 1 to 281)
AUTHORS Takahashi,T., Tanaka,M., Inazawa,J., Abe,T., Suda,T. and Nagata,S.
TITLE Human Fas ligand: gene structure, chromosomal location and species specificity
JOURNAL Int. Immunol. 6 (10), 1567-1574 (1994)
MEDLINE 95127560
PUBMED 7826947
REFERENCE 2 (residues 1 to 281)
AUTHORS Nagata,S.
TITLE Direct Submission
JOURNAL Submitted (06-JUL-1994) Shigekazu Nagata, Molecular Biology, Osaka Bioscience Institute, 4-6-2 Furuedai, Suita, Osaka, 565 Japan
COMMENT Method: conceptual translation.
FEATURES Location/Qualifiers
source 1..281
/organism="Homo sapiens"
/db_xref="taxon:9606"
/chromosome="1"
/map="1q23"
/dev_stage="adult"
Protein 1..281
/product="Fas ligand"
CDS 1..281
/gene="FasL"
/coded_by="U11821.1:65..910"
/note="similar to SwissProt Accession Number P36940"

ORIGIN

```
        1 mqqpfnypyp qiywvdssas spwappgtvl pcptsvprrp gqrrpppppp pppipppppp
       61 ppippipipp lkkrgnhstg lcllvmffmv lvalvglgig mfqlfhlqke laelrestsq
      121 mhtassleka ighpspppek kelrkvahlt gksnsrsmpl ewedtygivl lsgvkykkgg
      181 lvinetglyf vyskvyfrgq scnnlplshk vymrnskypq dlvmmegkmm syctTgqmwa
      241 rssylgavfn ltsadhlyvn vselslvnfe esqtffglyk l
```

//

Revised: July 5, 2002.